

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



PCT

To: GIDDINGS, Peter John GlaxoSmithKline CN925.1 980 Great West Road Brentford, Middlesex TW8 9GS GRANDE BRETAGNE		<div style="border: 1px solid black; padding: 5px; margin: 0 auto; width: 150px;"> Received 17 JAN 2005 MXG/FAX </div>	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)
Applicant's or agent's file reference MXGP33128		IMPORTANT NOTIFICATION Date of mailing 13.01.2005	
International application No. PCT/EP 03/11650	International filing date (day/month/year) 20.10.2003	Priority date (day/month/year) 22.10.2002	
Applicant GLAXO GROUP LIMITED		18 JAN 2005	
<div style="text-align: right; margin-bottom: 10px;">Received NESP</div> <ol style="list-style-type: none"> 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application. 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices. 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices. 4. REMINDER The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB301). Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned. For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide. The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims. 			
Name and mailing address of the international preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 </div> </div>		Authorized Officer Siefert, A Tel. +49 89 2399-2469	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference MXGP33128		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/11650	International filing date (day/month/year) 20.10.2003	Priority date (day/month/year) 22.10.2002	
International Patent Classification (IPC) or both national classification and IPC C07D209/26			
Applicant GLAXO GROUP LIMITED			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 05.05.2004		Date of completion of this report 13.01.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Schuemacher, A Telephone No. +49 89 2399-7818 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/1650

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-39 as originally filed

Claims, Numbers

1-23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/11650

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 19,21,22

because:

☒ the said international application, or the said claims Nos. 19,21,22 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-23
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-23
Industrial applicability (IA)	Yes: Claims	1-18,20,23
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/11650

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 19, 21 and 22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty, Article 33(2) PCT:

Reference is made to the following documents:

- D1: WO 02 076925 A (ELI LILLY AND COMPANY, USA) 3 October 2002
- D2: WO 02 24695 A (ORTHO MCNEIL PHARM INC) 28 March 2002
- D3: WO 02 12190 A (ORTHO MCNEIL PHARM INC) 14 February 2002
- D4: WO 00 06254 A (SOCIETE CIVILE BIOPROJET) 10 February 2000
- D5: WO 01 23374 A (SMITHKLINE BEECHAM) 5 April 2001
- D6: WO 01 066520 A (ONO PHARMACEUTICAL) 13 September 2001
- & EP 1 262 475 A 4 December 2002

In order to avoid any misunderstanding with regard to the content of D6, which is an International Patent Application in Japanese, its family-member patent EP 1262475 is used to assess novelty and inventive step of the present application.

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e bicyclic benzamide compounds of formula (I) according to claim 1, appears to fulfil the requirements of novelty, cf. Article 33(2) PCT:

The compounds of D2-D4 differ from the claimed compounds on account of the nitrogen containing heterocyclic moiety, which never encompass isoindoline, indole, tetrahydroisoquinoline or tetrahydro-1H-3-benzazepine.

The generic disclosures in D5 and D6 overlap with present claim 1 but these documents do not contain specific examples of compounds which fall under the scope of present claim 1 (in D6, all the examples differ from the claimed compounds because they always have an acetic acid group on the indole ring and in D5, all the examples miss the phenoxy group). D5 and D6 are therefore not considered to anticipate the subject-matter of the present application.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/11650

The subject-matter of present claim 1 is totally included in the generic disclosure of compounds of D1 (see claim 1 of D1). Since there is no specific example in D1 that falls under present claim 1, the subject-matter of the present invention could be considered as a novel selection of the compounds of D1; the selection consists in choosing an isoindoline, indole, tetrahydroisoquinoline or tetrahydro-1H-3-benzazepine ring among the possible nitrogen-containing heterocycle formed by the groups R⁷ and R⁸ according to claim 1 of D1.

Thus, the requirements for novelty of Article 33(2) PCT are considered to be met.

2. Inventive step, Article 33(3) PCT:

The present application relates to bicyclic benzamide compounds as histamine H3-receptor ligands, which can be useful in the treatment of cognitive impairments in neurological diseases.

Document D1, directed to histamine H3-receptor modulators, is considered as the closest prior art document. As the present application can be regarded as a novel selection of D1, the technical problem underlying the present invention has to be seen in the provision of compounds with affinity for the histamine H3-receptor which have an unexpected advantageous effect in comparison with the compounds of D1.

Nevertheless, there is no evidence in the present application proving that the claimed compounds provide an unexpected surprising effect compared to the compounds of D1 and that this unexpected effect has its origin in the selection of an isoindoline, indole, tetrahydroisoquinoline or tetrahydro-1H-3-benzazepine ring among the possible nitrogen-containing heterocycle formed by the groups R⁷ and R⁸ according to claim 1 of D1.

In the absence of evidence of an unexpected effect provided by a representative set of compounds as claimed, Article 33(3) PCT cannot be considered to be satisfied.

3. industrial applicability:

For the assessment of the present claims 19, 21 and 22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MXG/P33128	FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. PCT/EP 03/11650	International filing date (day/month/year) 20/10/2003	(Earliest) Priority Date (day/month/year) 22/10/2002
Applicant GLAXO GROUP LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

BICYCLIC BENZAMIDE COMPOUNDS AS HISTAMINE H₃ RECEPTOR LIGAND USEFUL IN THE TREATMENT OF NEUROLOGICAL DISEASES

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ **None of the figures.**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 03/11650

Box III TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/11650

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/26 C07D217/06 C07D209/44 C07D209/32 C07D215/08
 C07D403/04 C07D223/16 C07D409/04 C07D491/04 C07D403/12
 A61K31/4035 A61K31/404 A61K31/47 A61K31/55 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02 076925 A (ELI LILLY AND COMPANY, USA) 3 October 2002 (2002-10-03) cited in the application claims 1,14-19; examples 41-44,102,103,155,173 ---	1-23
Y	WO 02 24695 A (ORTHO MCNEIL PHARM INC) 28 March 2002 (2002-03-28) claims 1,23-25; examples 16,63-69 ---	1-23
Y	WO 02 12190 A (ORTHO MCNEIL PHARM INC) 14 February 2002 (2002-02-14) cited in the application claims 1,48-51; examples 9,31,54,76 --- -/--	1-23



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

13 January 2004

Date of mailing of the international search report

27/01/2004

Name and mailing address of the ISA

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 NL - 2280 HV Rijswijk
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Authorized officer

Schuemacher, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/11650

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 00 06254 A (SCHUNACK WALTER G ; SIGURD ELZ (DE); STARK HOLGER (DE); BIOPROJET S) 10 February 2000 (2000-02-10) cited in the application claims 79-81; examples 76,90,160 ---	1-23
Y	WO 01 23374 A (WYMAN PAUL ADRIAN ; MARSHALL HOWARD (GB); THOMPSON MERVYN (GB); SMI) 5 April 2001 (2001-04-05) cited in the application page 7, line 17 - line 31; claims 1,12,13 ---	1-23
A	WO 01 066520 A (ONO PHARMACEUTICAL) 13 September 2001 (2001-09-13) cited in the application -& EP 1 262 475 A 4 December 2002 (2002-12-04) examples 7(19) p.114, 7(24) p.117 and 7(54), p.132 page 9, line 35 -page 10, line 45; claim 1 ---	1-18,23
X,P	WO 02 094788 A (ELI LILLY AND COMPANY, USA) 28 November 2002 (2002-11-28) cited in the application examples 1-4 -----	1-18,23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/11650

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19,21-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/11650

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02076925	A	03-10-2002	CA 2441080 A1 WO 02076925 A2	03-10-2002 03-10-2002
WO 0224695	A	28-03-2002	AU 9293601 A CA 2423284 A1 EP 1326863 A2 WO 0224695 A2 US 2003013733 A1	02-04-2002 28-03-2002 16-07-2003 28-03-2002 16-01-2003
WO 0212190	A	14-02-2002	US 2002040024 A1 AU 8111901 A AU 8112101 A AU 8473301 A CA 2418369 A1 CA 2419027 A1 CA 2419036 A1 CZ 20030685 A3 CZ 20030686 A3 EP 1311499 A2 EP 1311482 A2 EP 1313721 A2 WO 0212224 A2 WO 0212214 A2 WO 0212190 A2 US 2002037896 A1 US 2002065278 A1	04-04-2002 18-02-2002 18-02-2002 18-02-2002 14-02-2002 14-02-2002 14-02-2002 13-08-2003 13-08-2003 21-05-2003 21-05-2003 28-05-2003 14-02-2002 14-02-2002 14-02-2002 28-03-2002 30-05-2002
WO 0006254	A	10-02-2000	EP 0978512 A1 EP 0982300 A2 AU 5511999 A CA 2321881 A1 WO 0006254 A2 EP 1100503 A2 JP 2002521463 T	09-02-2000 01-03-2000 21-02-2000 10-02-2000 10-02-2000 23-05-2001 16-07-2002
WO 0123374	A	05-04-2001	AU 765020 B2 AU 7783600 A BR 0014279 A CA 2385737 A1 CN 1399635 T CZ 20021038 A3 WO 0123374 A1 EP 1216239 A1 HU 0202787 A2 JP 2003510317 T NO 20021459 A NZ 517865 A TR 200200795 T2 ZA 200202319 A	04-09-2003 30-04-2001 21-05-2002 05-04-2001 26-02-2003 14-08-2002 05-04-2001 26-06-2002 28-12-2002 18-03-2003 22-03-2002 28-11-2003 22-07-2002 21-11-2002
WO 01066520	A	13-09-2001	AU 4106801 A CA 2402174 A1 CN 1427824 T EP 1262475 A1 HU 0301493 A2 WO 01066520 A1 NO 20024281 A US 2003176400 A1	17-09-2001 13-09-2001 02-07-2003 04-12-2002 28-08-2003 13-09-2001 08-11-2002 18-09-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/11650

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 01066520	A	ZA 200207031 A	06-03-2003
WO 02094788	A	28-11-2002 WO 02094788 A1	28-11-2002